Project Protocol

1. Title: Assessing the effectiveness and cost-effectiveness of oral nutritional interventions in malnourished frail elderly people

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2. Summary of Research

Background:

Malnutrition (or undernutrition) is very common in older people, affecting >1.3 million older adults (aged ≥65 years) in the UK.[1] Malnutrition contributes to £23.5 billion/year in Health and Social Care spend in the UK, over half of which is attributed to malnutrition in older adults.[1] Frail older people are much more likely to become malnourished than those without frailty.[2-5] Malnutrition worsens the health of frail older people, making them more vulnerable to longer stays in hospitals, readmissions, infections and delayed recovery.[3]

Finding effective ways of preventing malnutrition and reducing its adverse consequences is critical for improving the health of frail older people. Currently the recommended practice (e.g. NICE guidance) for treating malnutrition is to give dietary advice (help with meal planning, food fortification) and prescribed oral nutritional supplements (ONS).[6] However, guidelines and evidence reviews have not focused on frail older people. Moreover, several factors affect the compliance and acceptability of oral nutritional interventions amongst older people, carers and health professionals;[7-9] for example, loss of appetite, social isolation, physical disability, lack of resources – some of these issues were also highlighted by older people during our preparatory Public/Patient Engagement/Involvement (PPI/E) discussions. Assessing these factors is an important step in understanding active components that will aid in identifying what effective interventions look like, for example, how these are delivered, where and by whom; these aspects will be essential to inform the design of future intervention strategies.

Research Aim and Objectives:

The aim is to evaluate the effectiveness and cost-effectiveness of oral nutritional interventions in frail older people who are malnourished or at risk of malnutrition. We will further assess the evidence on the acceptability and components of these interventions.

Research objectives are to:

1. Systematically review a) the effectiveness and cost-effectiveness of different oral nutritional interventions in frail older people who are malnourished or at risk of malnutrition, and b) identify components of interventions that are associated with increased effectiveness or adherence.
2. Systematically review qualitative studies to assess issues related to acceptability of oral nutritional interventions amongst frail older people who are malnourished or at risk of malnutrition.
3. Undertake economic modelling to identify the cost-effectiveness of different models of oral nutritional interventions in frail older people who are malnourished or at risk of malnutrition, and value of information analysis to assess the value of future research.
4. Refine and develop a logic model for oral nutritional interventions (including determinants, components, outcomes) to reduce malnutrition in frail older people.
5. Collate findings and consult with stakeholders to identify: a) recommendations for interventions with potential for testing in future research; and b) implications for practice and policy.

Design: An evidence synthesis will be undertaken comprising systematic reviews, economic modelling and a logic model development. The logic model will be iteratively refined to illustrate determinants, intervention components, outcomes and adverse effects that emerge from the systematic reviews and economic analysis.
Crucially, the evidence synthesis will be informed by regular consultations with a PPI/E Reference Group (older people and carers) led by PPI/E Co-applicant (Elders' Council Newcastle), and other stakeholders (e.g. dieticians, clinicians, topic experts, policy makers).

Setting: All settings including community and hospital settings will be included.

Target population: This will include frail older people (≥65 years) who are able to swallow and are malnourished or at risk of malnutrition.

Health technologies to be considered: Oral nutritional interventions including prescribable oral nutritional supplements (ONS) with or without dietary advice, and food fortification (e.g. protein, carbohydrate and/or fat, vitamins).

Strategy for systematic review and economic analysis: Three related systematic reviews will be conducted to assess: 1) the effectiveness of oral nutritional interventions and their components in frail older people; 2) issues related to acceptability, adherence and compliance (for example, barriers, facilitators, psychosocial factors) to these interventions; 3) published economic evaluations. Validated frameworks (e.g. Theoretical Domains Framework and Consolidated Framework for Implementation Research) will be utilised to identify determinants and components of interventions in the evidence synthesis.[10 11] Informed by the three reviews, a decision-analytic model will be developed to estimate the cost-effectiveness of alternative oral nutritional interventions, followed by a Value of Information analysis to explore future research needs.

Research outputs and impacts: Project outputs include evidence on the most effective (or potentially effective) oral nutritional interventions, including their components, how and where these are delivered, and the potential cost implications. This will provide a comprehensive picture of the current evidence base, and the basis for further research and recommendations for practice and policy. A logic model presenting these components and pathways to reducing malnutrition in frail older people will also be a key output to aid researchers, practitioners, and decision makers.
The long-term goal is to identify interventions that can prevent or treat malnutrition, thereby reducing its impact on health and social care services, and improving the lives of frail older people.

Project timetable/ team: The project will be conducted over an 18-month period. A Gantt chart is presented in figure 4 below. The team comprises expertise from public health, primary care, healthy ageing, service users, nutrition and diet, evidence synthesis including statistical methods for exploring heterogeneity, and health economics.

3. Background and Rationale

Problem being addressed: Malnutrition and frailty in older people in the UK
The UK population is ageing rapidly. The number of people aged 65 years and over is set to increase from 12% in 2016 to 18% by 2041 and further to 26% by 2066, with the fastest growth expected in the ≥85 years group.[12] Ageing is associated with increased risk of multimorbidity,[13] and disability,[14] which represents a major challenge for future health and social care service provision and funding.[15] There is a critical need to identify effective interventions to mitigate age-related morbidity in populations who are likely to benefit most. Chronic undernutrition or malnutrition is an important contributor to morbidity and mortality in older adults and is amenable to treatment, therefore providing a potential target for intervention.

Malnutrition is the deficiency of energy, protein, vitamins and minerals which causes weight loss, muscle loss and functional limitations,[6] and is common among older adults ≥65 years. Over 1.3 million older UK adults are estimated to be malnourished, or at risk of malnutrition.[1] While malnutrition affects <10% of independent community-dwelling older adults,[16] prevalence is much greater in settings where there are increased care needs.[17] National surveys have detected malnutrition in 28% of hospital admissions, 27% of residential care home residents and 41% of nursing home residents.[18] Malnutrition has serious adverse consequences including physical decline, and poorer outcomes of diseases and increased complications, such as infections, delayed recovery, hospital readmissions, increased length of hospital stays, more GP visits, and poor quality of life and well-being.[1 19] Malnutrition and its consequences are estimated to contribute to at least £23.5 billion or >15% of total Health and Social Care expenditure in the UK; older adults (≥65 years) account for 52% of the total costs of malnutrition.[1]

Frail older people are at a particularly high-risk of malnutrition and are three to four times more likely to be malnourished.[2-5]. Frailty is conceptualised as an abnormal health state relating to loss of biological reserves causing increased vulnerability to small environmental or health changes, which can lead to disability, falls, long-term care, hospital admissions and mortality.[20 21]. Around one in ten people over 65 years and around a quarter to a half of people over 85 years are living with frailty.[20] Malnutrition and frailty are closely inter-linked. As shown in Figure 1, poor nutritional status and weight loss increase the risk of frailty, [22] and the presence of malnutrition further worsens the health status of frail older people.[3] Nutrition supplementation is recommended as one of the mainstays of intervention in treating frailty (ESPEN) however much of the evidence is based on short-term protein synthesis studies or micronutrient interventions (e.g. amino acids, omega 3, vitamin D) which have not shown consistent benefits on muscle mass and function.[22] Furthermore, a micronutrient treatment approach is unlikely to benefit malnutrition and broader clinical and functional outcomes that are important in frailty.

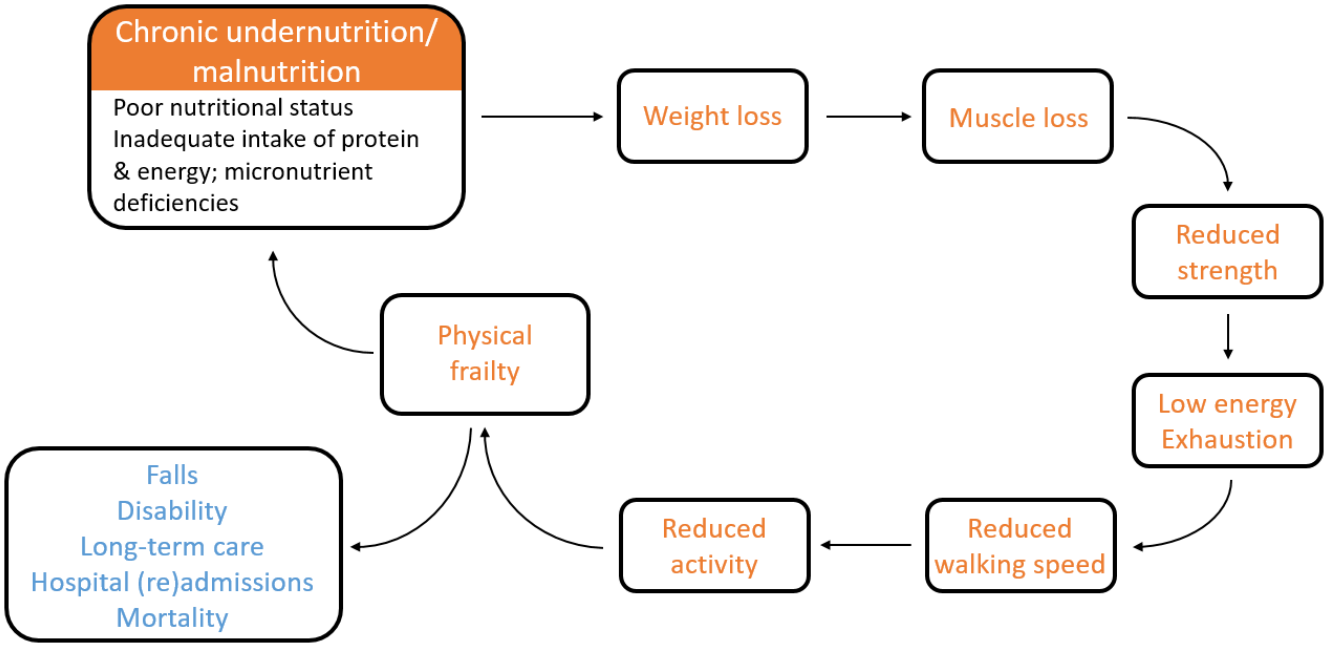


Figure 1: Linkages between malnutrition and frailty in older people (adapted from Xue et al)[21]

Why this research is needed now

With a rapidly ageing population in the UK, frailty and malnutrition pose health and social care challenges.[20] Preventing malnutrition is critical to improving the health of frail older people. However, malnutrition remains largely unrecognised and untreated in older people. There is poor awareness and little consensus among health and social care professionals and the general public on effective ways to prevent or treat malnutrition in frail older people.

Our research addresses the evidence gaps highlighted in the NIHR Health Technology Assessment (HTA) commissioning brief on oral nutritional interventions in malnourished frail elderly. This call draws on research recommendations highlighted in the National Institute of Health & Care Excellence (NICE) Guidelines CG32 on nutritional support for adults who are malnourished or at risk of malnutrition.[6] These NICE Guidelines and other clinical pathways recommend oral nutritional support for those malnourished or at risk of malnutrition.[6 23 24] Oral nutritional support includes dietary counselling (meal adaptation, advice on food intake, food fortification), and prescribed oral nutritional supplements (ONS).[6] However, a key research gap highlighted in current guidelines, is evidence specifically amongst frail older people on oral nutritional interventions which are effective in reducing malnutrition.

Further, our project is based on the feedback of an unmet need from older people and carers as part of our preparatory PPI/E discussions. The discussions highlighted the need to investigate issues related to poor nutrition in older people, for example affordability and compliance, to move beyond understanding what works, but also how it works and for what groups of older people. They also emphasised the need for PPI/E input in interpreting findings and developing recommendations that are relevant for older people and for policy makers. A couple of quotes reflect these issues - "*I don't know what really works for better food and nutrition*." "*My aunty has these powders (supplements) but it sits in her cupboard, she doesn't like them.*" "*Issues such as affordability, availability of help from dieticians, loneliness are important for older people. The wider environment needs to be considered with supplements."* These key issues have informed and shaped the scope of our project.

Review of existing evidence

The recent evidence gaps summarised in the HTA commissioning brief and NICE guidelines (CG32) have provided us a starting point for this work. NICE and other clinical guidelines recommend oral nutrition support for people who are malnourished or at risk of developing malnutrition to include one or more of the following approaches: support for people unable to feed themselves, advice from a dietitian, altered meal patterns, fortified food (protein, carbohydrate and/or fat, minerals and vitamins) and prescription of oral nutritional supplements (ONS) where appropriate. Previous studies have found nutritional interventions, including ONS, to be effective in reducing malnutrition in community and hospital settings.[25 26]

Evidence from reviews so far suggest that prescribed ONS is effective in reducing malnutrition, and its consequences such as delayed wound healing and infections.[9] ONS is often viewed as an appropriate mode of managing malnutrition when it is difficult for individuals to consume energy and/or nutrients from food; for example in case of acute illness or lack of availability of food.[9] Systematic reviews have also reported the cost-effectiveness of ONS in the management of malnutrition.[25-27] Cost-effectiveness evidence suggests that the use of ONS in community settings can reduce hospital stays and admissions (estimated savings ≥£119,200 per 100,000 people).[1]

However, individual study findings are not entirely consistent for clinical outcomes likely owing to differences in the type of ONS evaluated and study methodology.[28] Evidence is mainly derived from small trials conducted in heterogeneous populations and across healthcare settings. Some reviews have included only hospital patients post-surgery,[29 30] others have focused on community-dwelling adults,[31] and mixed populations,[32,33,34] – this makes it difficult to draw conclusions on the effectiveness of ONS for high-risk populations such as frail older people.

A further gap in knowledge is whether prescribed ONS offer additional benefits above other oral nutrition support strategies such as fortified food or expert dietary advice. Dietary counselling is often the first means of nutritional interventions in practice.[8] This includes supporting older people with planning their diet and making meal plans, and is delivered by dieticians in the community or in hospitals. Food fortification including adding specific nutrients (e.g. vitamins, proteins) to the diet is another form of oral nutritional support. However, while ONS has also been shown to be cost-effective, the costs of other forms of nutritional support, including dietary advice, food snacks and food fortification, to manage malnutrition remain unclear and need to be elucidated.[9] The evidence on ONS has largely informed the guidelines on malnutrition management. However, these reviews have mostly compared ONS with routine care (i.e. no nutritional support), not necessarily with dietary advice.[9]

In summary, much of the focus of previous reviews on oral nutritional interventions include adult populations of all ages, not just frail older people. Moreover, previous reviews and studies have mostly looked at interventions to treat malnutrition related to diseases (such as cancer, HIV) and surgery, which will have different underlying mechanisms to malnutrition in frail older people. The evidence in current guidelines is also mostly from studies on disease-related malnutrition.[23 24] As

noted by topic experts in the NICE CG32 guidelines, there is a lack of emphasis on effective interventions to reduce malnutrition among frail older people.

Determinants of malnutrition in frail older people: understanding factors affecting adherence to and acceptability of interventions

Effective treatment and management of malnutrition will need to be tailored to frail older people. Malnutrition is multi-factorial. In addition to co-morbidities, several other factors affect the nutrition of older people. These include physiological changes with ageing (loss of appetite, poor taste and smell, disability), psychosocial aspects (social support, resilience, lack of knowledge about food) and personal resources (poverty, inability to shop for food).[35-38] These factors then lead to slower eating, and lack of diet variety, which in turn leads to poor dietary intake (low calorie, protein, and key nutrients) and ultimately a state of malnutrition.[8] These issues were highlighted in our PPI/E discussions as being important in influencing on how much and how well older people eat.

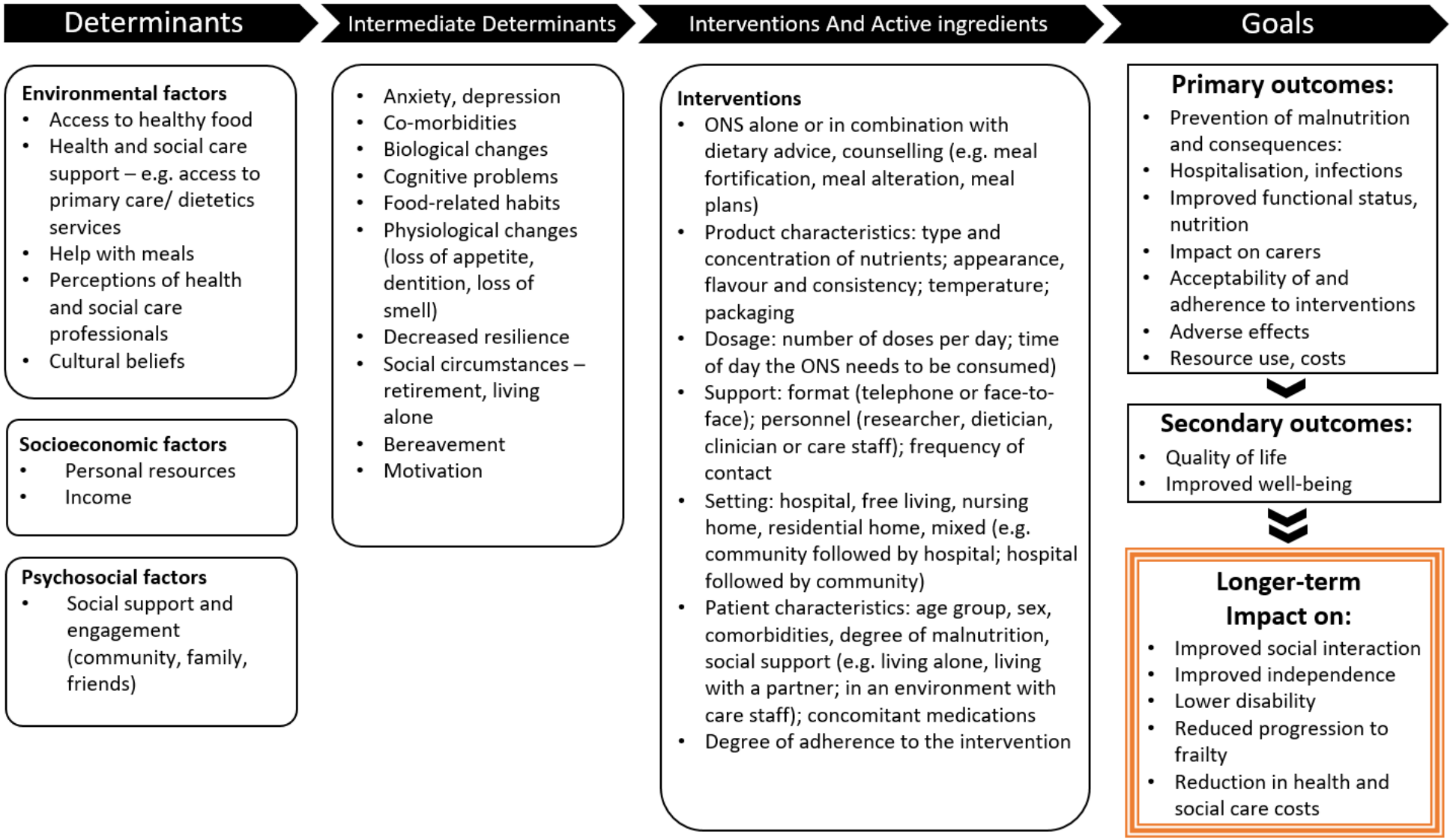
Issues of compliance and acceptability also play a crucial role in inadequate nutritional support.[8 9 39] While ONS have been found to be effective, their uptake and compliance can be poor. Taste, texture, temperature and mode of ONS (liquid, powder) all influence the extent to which ONS are consumed, particularly over prolonged periods of time. For example, change in energy density can improve compliance and uptake of ONS.[9] Similar issues of compliance are also relevant for dietary advice and counselling to ensure that diet plans are acceptable and sustainable over time. Delivery and implementation of nutritional support by clinicians and healthcare professionals can also be very variable.[39] This could be due to lack of consistency in guidelines on whether ONS with or without dietary advice is effective in older people.[39] Clinical practice has been reported by dietitians to be influenced by lack of knowledge, ease of implementation, published research, and local departmental protocols.[39] Understanding ways to improve the adoption and implementations of evidence-based nutritional support interventions into routine practice is a particular gap in the existing evidence.

Rationale for proposed research and methods

Our proposed research is aimed at addressing the question in the commissioned HTA brief and the gaps in evidence and research needs as highlighted above. In order to keep to the HTA commissioned brief, our research will not focus on wider interventions such as physical activity along with nutritional interventions, to improve outcomes in frail older people.

The key clinical and research needs our project addresses are to identify: 1) effective (or potentially effective) oral nutritional interventions in frail older people; 2) ways to address uptake and implementation of oral nutritional interventions; 3) cost-effectiveness of interventions (including ONS and dietary advice) in frail older people. To address these gaps, we will review and synthesise evidence on effectiveness, cost-effectiveness and acceptability of oral nutritional interventions in frail older people, in consultation with older people, clinicians and policy makers. We will refine a logic model which will illustrate pathways, components, and outcomes including intermediary outcomes.[40] Our initial logic model (Figure 2) draws on current evidence and feedback from our preparatory PPI/E work. At all stages of the project, the logic model will be iteratively refined with emerging findings along with input from stakeholders to produce a final logic model by the end of the project. The logic model will act as an aid for further research and for practitioners and commissioners to aid in decision-making.

Figure 2: Initial logic model to conceptualise the evidence synthesis of oral nutritional interventions to reduce malnutrition in frail older people



We will conduct an evidence synthesis that will focus on assessing the (potential) effectiveness of different oral nutritional interventions, including prescribable ONS and dietary advice, specifically in frail older populations. As part of the first systematic reviews on effectiveness, and the second on acceptability, adherence and compliance, we will investigate what might be 'active components' of nutritional interventions. Given the multi-faceted nature of oral nutritional interventions, the identification of specific components (active components) of the intervention which contribute to outcomes is necessary to inform the development and appropriate targeting of effective interventions in older people. Active components will be elements of the oral nutritional intervention which aids in the delivery and implementation of the intervention, and typically include aspects that can be altered or modified to achieve better effectiveness. Active components would include elements such as how the intervention was delivered, by whom, timings, any behaviour change techniques.[8 9 41] Specific aspects of ONS interventions include energy density, flavours, textures and temperature, which can influence compliance. We will also assess mediating factors and determinants underlying oral nutritional interventions and improved outcomes in frail older people. Mediators will include psychosocial factors (social isolation, depression), physical resources, socioeconomic factors (economic capability), and access to services.[8 37] These issues (i.e. barriers, facilitators) are particularly relevant for frail older people because of the wide ranging factors that influence their nutritional status.

Understanding these determinants and causal mechanisms will help identify ways in which effective interventions can be delivered. Our evidence synthesis will therefore include both quantitative studies with data on effectiveness as well as qualitative studies investigating acceptability, compliance and uptake of interventions. There is a greater recognition for the explicit use of theory to investigate facilitators and barriers to change and implementation, and to understand the mechanisms of change and the contexts in which interventions are effective.[42] While undertaking the systematic reviews in this project, we will apply validated frameworks to specify components and determinants of oral nutritional interventions in frail older people. These frameworks include the Theoretical Domains Framework (TDF),[11] and the Consolidated Framework for Implementation Research (CFIR),[10] which aid in improving the implementation of interventions. The TDF has been developed and applied to understand change and determinants of behaviours of health professionals as well as of populations, for example loneliness in older adults. The CFIR provides as overarching typology to promote implementation theory development and to understand what works where and why across multiple contexts. We plan to apply both the TDF and CFIR frameworks as they are complementary.[43] The CFIR emphasises predominantly the collective domains (e.g. settings, context, process), while the TDF has more insights on individual-level constructs of interventions (e.g. behaviour, skills, motivation, resources). Using the CFIR and TDF will allow fully defining the different determinants and levels of behaviour change. This will help provide greater clarity and understanding of the components of effective interventions and how these work to reduce malnutrition in older people. CFIR and TDF have been applied in systematic reviews to guide the coding framework, refine the theoretical framework and to synthesise findings from quantitative and qualitative studies.[44-48] Analytical approaches such as meta-regression will be used to systematically examine components and determinants as part of the evidence synthesis. Based on the systematic reviews and input from PPI/E and Advisory Groups, we will also undertake an economic evaluation to establish a better understanding of the cost implications of potentially effective interventions. We will also conduct a value of information (VoI) analysis to identify key future areas of research.

An integral part of our project will be input from older people and other key stakeholders. A PPI/E group will be established and led by our Co-applicant from Elders Council. This group will meet face-to-face three-monthly and will be consulted for input into the scope of reviews, emerging findings and interpretation of findings. Another Advisory Group including our PPI/E Co-applicant, clinicians, healthcare professionals, topic experts in frailty, nutrition and policy makers will also provide regular input. This input from stakeholders will also be used to iteratively refine the logic model. A final logic model will be produced based on findings from the systematic reviews, economic analysis and stakeholder input. Our research findings will help inform future research and highlight implications for clinical practice to reduce malnutrition in frail older people.

4. Aims and objectives

What are the research aims and objectives?

The aim is to evaluate the effectiveness and cost-effectiveness of oral nutritional interventions in frail older people who are malnourished or at risk of malnutrition. We will further assess the acceptability and components of these interventions.
The goal of our study is to develop recommendations in consultation with older people, practitioners and policy makers for future interventions, and implications for practice to reduce malnutrition in frail older people.

The objectives are to:

1. Systematically review a) the effectiveness and cost-effectiveness of different oral nutritional interventions in frail older people who are malnourished or at risk of malnutrition, and b) identify components of interventions that are associated with increased effectiveness or adherence.
2. Systematically review qualitative studies to assess issues related to acceptability of oral nutritional interventions amongst frail older people who are malnourished or at risk of malnutrition.
3. Undertake economic modelling to identify the cost-effectiveness of different models of oral nutritional interventions in frail older people who are malnourished or at risk of malnutrition, and value of information (VoI) analysis to assess the value of future research.
4. Refine and develop a logic model for oral nutritional interventions (including determinants, components, outcomes) to reduce malnutrition in frail older people.
5. Collate findings and consult with stakeholders to identify: a) recommendations for interventions with potential for testing in future research; and b) implications for practice and policy.

5. Research Plan / Methods

The study will be conducted in three phases, with PPI/E involvement and refinement of the logic model throughout. These are illustrated in Figure 3.

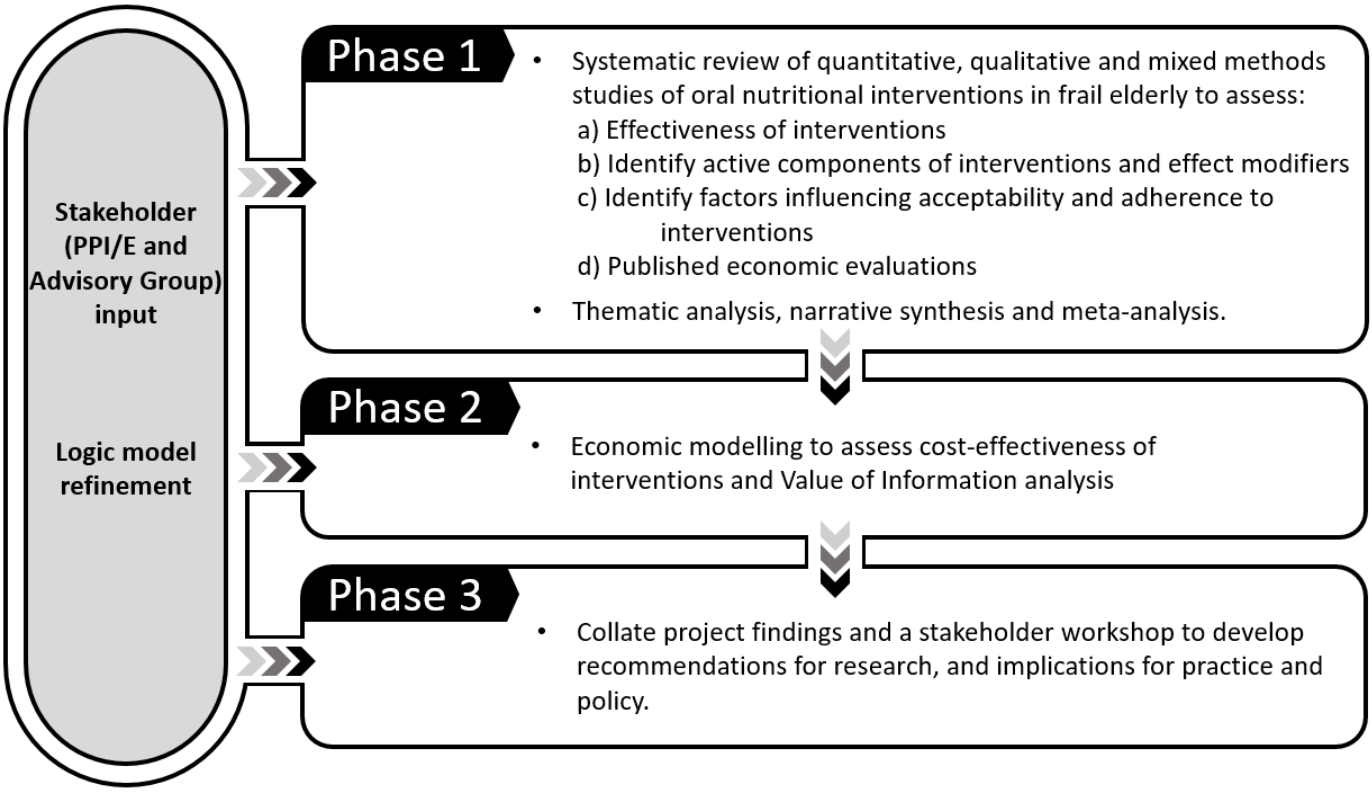


Figure 3: Overview of phases of project plan

5.1 PPI/E Reference Group and Review Advisory Group

We will regularly consult our PPI/E Reference Group and Review Advisory Group on the scope of the review, relevant data sources, interpreting findings, formulating recommendations and dissemination.

Our PPI/E Reference Group will include 4-5 older people (≥65 years) from Voice (PPI/E group at Newcastle University Institute of Aging) and Elders' Council, Newcastle, which will meet every three months. Our PPI/E Co-applicant (Raffle) will lead PPI/E consultations and feedback their views to the Advisory Group.

The Review Advisory Group includes Elders Council Newcastle (Barbara Douglas), Food Nation (Nicola Cowell), clinicians leading on frailty and malnutrition (Lesley Bainbridge: Frailty Clinical Network Lead North East & North Cumbria; Margot Gosney: Care of the Elderly Consultant with expertise in malnutrition, Reading; Robyn Collery: dietician NHS Vanguard Programme); Public Health England (Elaine Rashbrook); and research experts in nutrition and malnutrition (Ashley Adamson, Newcastle; Paul Little, Southampton).

5.2 Design and theoretical/conceptual framework and logic model refinement

An evidence synthesis study design informed by input PPI/E and other stakeholders will be used. The study design will incorporate the following components: 1) a systematic review of quantitative, qualitative and mixed methods studies to assess a) effectiveness of interventions, b) to identify active components of the intervention and effect modifiers using validated frameworks (e.g. Theoretical Domains Framework and Consolidated Framework for Implementation Research (CFIR)); c) to identify factors influencing acceptability and adherence to interventions; d) published economic evaluations. 2) Economic modelling will be undertaken to estimate the cost-effectiveness of oral nutritional interventions, and Value of Information (VoI) analysis will be undertaken to assess the value of future research. 3) Collate project findings and a stakeholder workshop with our PPI/E Reference Group, and Review Advisory Group (older people, clinicians, research experts, policy makers), to develop recommendations for research, and implications for service delivery and policy.

Throughout the project, a logic model will be refined and developed to illustrate determinants, components and outcomes, including intermediary and long-term goals in reducing malnutrition in frail older people. It will help conceptualise factors underpinning interventions that can potentially reduce malnutrition and improve outcomes in older people. The logic model will be used to explicitly lay out causal mechanisms underlying malnutrition in frail older people, as well as the potential for interventions, contextual factors and potential harms or unintended outcomes of interventions. As suggested by Anderson et al, we will use the logic model to guide the systematic reviews and refine the scope of the reviews.[40] We have started to build an initial logic model based on our scoping search and input from PPI/E discussions (figure 2), which will act as a starting point for further development during the project.

The logic model will be refined, tested and challenged at every stage based on findings from the evidence synthesis and stakeholders' input. We will seek input from older people and carers through our PPI/E Reference Group, and from our Review Advisory Group comprising clinicians, charities, academic experts and policy representatives (e.g. NHS England, third sector, Public Health England). The logic model will help provide a deeper understanding of why and where interventions work (or not) and not just whether interventions are effective or ineffective.[40] Understanding these issues with the aid of a logic model will ensure that our research and findings are relevant to older people and for policy and practice. In the final stage of the project, we will draw together our findings and finalise the logic model. The logic model will be a useful aid in drawing recommendations and implications of findings as part of the workshop with stakeholders in the final phase of this project.

5.3 Health technologies being assessed

Oral nutritional interventions are defined as prescribable ONS with or without dietary advice, food fortification (e.g. with protein, carbohydrate and/or fat, plus minerals and vitamins), altered meal patterns. Active components of these interventions, such as timing, delivery, and type of ONS, determinants (barriers, facilitators) and behaviour change techniques will also be assessed.

5.4 Detailed methods

5.4.1 Phase 1: systematic reviews of the effectiveness and cost-effectiveness of oral nutritional interventions in malnourished, frail older people and to identify issues related to acceptability and adherence to interventions

Protocol development
A protocol for the systematic review will be developed using PRISMA-P criteria.[49] Evidence synthesis will be conducted using the Centre for Reviews and Dissemination guidance,[50] and reported on PROSPERO using PRISMA guidelines.[51]

Search strategy
The following databases will be searched: Medline, EMBASE, Open Grey, The Cochrane Library and Clinicaltrials.gov, ProQuest Dissertations and Theses. Additional databases include the Health Management Information Consortium, NHS Economic Evaluation Database (until December 2014), and Cost-Effectiveness Analysis Registry. The RAG will be consulted on relevant third sector sites. An experienced information specialist will develop and implement the searches. We will hand-search bibliographies of included studies, and conferences and key journals not indexed in the databases.

Study selection
The review inclusion criteria are as follows:

Target population*:* frail older people (≥65 years) able to swallow and malnourished or at risk of malnutrition; frailty defined as any standardised measure such as the Fried frailty phenotype, frailty index or cumulative deficit model;[52 53] malnourished or risk of malnutrition defined as under-nutrition as per NICE guideline CG32, and assessed by standardised tools (e.g. MUST, Mini Nutritional Assessment (MNA), MNA-Short Form. All settings (e.g. community, hospitals) will be included. Studies of participants with dysphagia (inability to swallow), specific diseases (e.g. cancer, HIV) or immune-nutrition or satiety hormone suppression, will be excluded.

Interventions: Prescribable ONS with or without dietary advice/counselling and active components of these interventions, such as timing, delivery, and type of ONS, and behaviour change techniques will be included. ONS are multi-nutrient products (ready-made liquid, pudding or powder to be mixed with fluids) containing a mix of macronutrients (protein, carbohydrate, fat) and micronutrients to increase energy and nutrient intakes of individuals with malnutrition or at nutritional risk.[9] Dietary advice includes modifying food intake, food fortification or meal alteration to improve nutritional intake.[6] We will also assess components of the intervention, factors which modify and mediate the effectiveness of interventions and determinants of adherence to interventions (e.g. such as timing, delivery, and type of ONS, and behaviour change techniques (BCTs), behavioural, social or economic factors). Disease-specific ONS (e.g. modified to be suitable for disease-specific populations such as renal, liver or critical care patients) will be excluded. In order to reduce potential heterogeneity, studies of non-commercial or home prepared ONS formulations with only macronutrients rather than balance of energy, protein, micronutrients and trace elements, will be excluded. We will also exclude artificial nutritional support e.g. delivered via the enteral or parental route.

Comparator groups: Studies will be included if there is any comparison group. The comparison group could include: ONS alone versus standard care, dietary advice or no intervention; ONS plus dietary advice versus standard care/no intervention; ONS plus dietary advice versus dietary advice alone. Studies will be excluded if there is no comparison group.

Outcomes: Primary outcomes include malnutrition and its adverse consequences, including markers of nutritional status (weight, BMI, muscle mass, fat free mass), morbidity, and complications (e.g. infections, delayed wound healing, hospital admissions), functional status and its changes (disability, physical performance, muscle strength), markers of frailty, quality of life and well-being, and mortality. Outcomes will also include impact on carers, acceptability of, wastage, resource use, cost-effectiveness, and any adverse effects. Aspects related to adherence to interventions will also be assessed, such as initiating the use of interventions, persistence or compliance, duration of use of interventions, and factors affecting compliance.

Study design: Randomized controlled trials (RCTs individually and cluster randomized); non-randomized controlled studies, such as observational studies including cohort studies, case-control studies, cross-sectional studies, case series and case studies; qualitative studies; mixed methods studies and economic evaluations.[54]

Language, country and date: no language, geographical or date of publication restrictions will be applied.

Size of the evidence base
Our scoping search suggests a clearly identifiable literature for a systematic review. A scoping search in Medline and Embase, undertaken in November 2018 and updated in May 2019, yielded 4,144 records. A trial screening of a sample of these results, revealed nine relevant studies. These included five RCTs, which assessed the effectiveness of multi-nutrient supplements alone or in addition to dietary counselling or snacks and food fortification, on a range of outcomes, including economic outcomes, in frail elderly persons from hospital, community or nursing home settings.[55-59] One of the RCTs incorporated an economic evaluation of the intervention.[59] A prospective observational study was identified which evaluated the impacts of a multi-nutrient oral nutritional supplement on the physical function, nutritional status, and quality of life amongst frail institutionalised older adults.[60] A cross-sectional study was identified which assessed the effects of dietary supplementation on the nutritional status of malnourished, fragile nursing home residents.[61] A qualitative study investigated individual-level factors relating to ONS consumption.[62] A mixed-methods study assessed the degree of compliance, factors influencing compliance, views and attitudes of elderly patients and their health professionals in relation to prescribed ONS.[63] In a full search in additional databases, we expect to find a larger volume of relevant literature.

Study selection
Studies will be independently assessed in Rayyan by two reviewers using the review inclusion criteria. An initial 10% of titles and abstracts will be screened; disagreements will be discussed between reviewers to clarify the inclusion criteria. Any disagreements will be discussed further with a clinician team member. If necessary this process will be repeated. Once consensus is achieved, both reviewers will commence independent screening. Disagreements in screening decisions will be resolved through discussion or consultation with a third reviewer (Principal Investigator (PI)). All studies judged as relevant based on title and abstract will be obtained as full texts.

Data extraction
Data from each included study will be extracted using a bespoke form, which will be designed and piloted to ensure that it is suitable for the range of study designs included in the review. Extracted data will include citation, aims/objectives, study design and analysis, participant characteristics, details of the intervention(s), including active components, effect modifiers and determinants of adherence (e.g. initiation of interventions, duration of use) informed by TDF and CFIR frameworks which offer complementary domains. The TDF framework will help unpack individual-level domains

(e.g. behaviours, skills), while CFIR focuses on collective or system-wide domains (e.g. settings, context, process). We will use established frameworks such as the ISPOR working group's definitions to identify issues related to compliance and persistence and adherence.[64] Data extraction will also include comparator(s), outcome(s) and outcome measures, and results. The data extraction form will be piloted on a representative sample of studies to ensure that all relevant information is captured. Study authors will be contacted for further information in situations where insufficient information is available to extract all required information. Data extraction will be undertaken by one reviewer and checked by a second reviewer. Discrepancies will be resolved by consensus or consultation with a third reviewer (PI).

Quality assessment
Risk of bias in studies will be assessed using established tools, i.e. Cochrane Risk of Bias tool (v 2.0) for RCTs, and ROBINS-I for non-randomized studies.[50 54 65] Qualitative studies will be assessed using the Critical Appraisal Skills Program tool.[50] Economic studies will be quality appraised using the Consolidated Health Economic Reporting Standards checklist,[66] or NICE quality appraisal checklist,[67] and the appropriate risk of bias tool appropriate to their underlying study design (experimental or observational). Study authors will be contacted for further information in situations where insufficient information is available apply quality appraisal criteria to particular studies.

Data synthesis
Studies included in the review will be synthesised thematically (qualitative data), using a narrative synthesis framework (quantitative and qualitative data) and using meta-analysis (quantitative data). A coding framework will be developed that encompasses domains from the TDF and CFIR frameworks (including aspects related to adherence). Two researchers will independently map raw data such as participant quotations in the qualitative studies, and the results from statistical analyses in quantitative studies, to the TDF and CFIR domains. Independent coding will be compared and discrepancies resolved via discussion and adjudication by a third person (PI) where necessary. The frequency with which domains from the TDF and CFIR are identified within and across included studies will be assessed and tabulated.
Thematic synthesis will be applied to qualitative studies. From the TDF and CFIR coding of the qualitative data, themes will be identified to add contextual interpretation using the stages outlined by Thomas and Harden (2008).[68] This is a three-stage process involving adding codes to the data line by line, identifying core descriptive themes and providing interpretive analytical themes. Codes to the text will be added using NVIVO software, from which descriptive and analytical themes are identified. Quantitative data will be mapped to the qualitative themes in tables, to facilitate triangulation of the data. Results from quantitative and qualitative studies will be synthesised using a narrative framework.[69] This synthesis will be conducted in four main stages, including developing a theory of how oral nutritional interventions and their constituent (active) components influence health and social outcomes in malnourished frail elderly persons, why and for whom; developing a preliminary synthesis of findings of included studies; exploring relationships in the data; and assessing the robustness of the synthesis.

Quantitative analysis
Meta-analyses will be undertaken if appropriate. A full protocol for conducting meta-analyses will be developed at the start of the project. There is likely to be significant heterogeneity, consequently random-effects meta-analyses will be conducted. However, we anticipate where feasible that outcome data, both effect and quality of life outcomes, extracted from studies will be combined using appropriate meta-analytic methods: Mantel-Haenszel for odds ratios from dichotomous data, weighted mean difference (or standardised weighted mean difference if different metrics are used) for continuous outcomes, generic inverse variance method for time to event data. The heterogeneity statistics, I-squared, tau-squared and the chi-squared test, will all be reported along with the uncertainty in I-squared and tau-squared.

To fully exploit the data, if feasible, a series of analysis will be undertaken using both pairwise and network meta-analysis methods (NMA). The NMA will enable the combination of both direct and

indirect evidence to allow an estimate of comparative effectiveness of the included interventions. We will again use a random effects model given there will be heterogeneity between the studies. A common heterogeneity variance across all the comparisons will be assumed and multi-arm trials will be included with an adjustment for potential correlation between arms. In the base case we will assume additivity of component effects, i.e. that the total effect of composite interventions is equal to the sum of each individual component, however we will test this additivity assumption in sensitivity analysis. The initial analysis will be at the intervention level. However, if feasible and warranted, we will undertake a component level NMA; component NMA can be used to disentangle the treatment effects of different components included in composite interventions. All analyses will be undertaken in WinBUGs.

Meta-regression, sensitivity analysis and subgroups
Potential sources of heterogeneity and/or inconsistency will be investigated using meta-regression or sensitivity analysis to assess any impact on derived effect estimates. Where data allow, sub-group analysis according to participant characteristics (e.g. age group (<85 or ≥85)) will be undertaken. Effect modifiers will be investigated, for example, active components (e.g. clinical support), ONS characteristics, socioeconomic status, co-morbidities and level of frailty (see initial logic model in figure 1).

Phase 2: Cost-effectiveness modelling

In this phase, we will undertake economic modelling to identify the cost-effectiveness of different oral nutritional interventions in frail older people, and VoI analysis to assess the value of future research.

A decision-analytic model will be developed to estimate the potential cost-effectiveness of alternative oral nutritional interventions in frail elderly who are malnourished, or at risk of becoming malnourished.

The model will be informed by reviews of economic evaluations, quantitative and qualitative evidence undertaken in phase 1. It will be developed in consultation with clinical and PPI/E representatives to ensure that it reflects current practice and the course of the clinical condition. The model will assess the costs and health consequences, measured in terms of quality-adjusted life years (QALYs), of alternative interventions and will allow for the extrapolation of costs and outcomes over the lifetime of the patient. Information on unit costs associated with relevant health care services and treatments will be derived from routine sources including the Personal Social Services Research Unit, the British National Formulary and NHS Reference Costs.[70-72] QALYs associated with the alternative health care strategies will be estimated using utility values derived from the literature, along with time spent in specific modelled health states. The results of the model-based economic evaluation will be presented in terms of incremental cost per QALY gained, i.e. a cost-utility analysis. The model will be developed in accordance with the NICE reference case, and will capture the clinical process of the condition, characterise participants' treatment pathways and the impact of alternative oral nutritional interventions.[73]

If feasible, effectiveness estimates for individual components of interventions being compared in the economic model will be derived from the component level NMA. Alternative intervention 'packages' can then be compared by evaluating different combinations of potentially effective components. The impact of active components and effect modifiers on the effectiveness of different treatments may therefore be captured in the economic model. Intervention 'packages' that are ultimately considered to be of potential value for money based on the model output will be cross-validated against effectiveness estimates derived from the behavioural analysis being conducted; enabling a linking of these data will help explore the impact of the TDF/CFIR on cost-effectiveness rankings. Where a component level NMA is not feasible, the economic modelling will be informed by the using meta-regression results of the TDF/CFIR analysis. Although this will not provide the same outcomes, it will enable the probability of the TDF/CFIR components being cost-effective to be estimated. The latter approach will build on methods developed in a recent NIHR HTA.[74] As part of the economic analysis, adherence to oral nutritional interventions will also be considered in terms of both persistence and

compliance. Persistence is the duration of time from initiation of treatment to discontinuation, while compliance relates to how well the participant conforms to the recommendations made by the provider in relation to timing, dosage and frequency of treatment use. The impact of both persistence and compliance on the efficacy of individual treatments and on participants' health outcomes will be applied in the economic model. The economic analysis will be carried out from the perspective of the UK NHS and Personal Social Services (PSS) to take into account health care costs as well as longer-term social care costs. In the base-case, both costs and QALYs will be discounted at a rate of 3.5% per year (NICE technology appraisal guide).[73]

We anticipate the model will be an individual-level state transition model. This is likely to be the most appropriate model as it will capture varying individual characteristics which are likely to have a non-linear relationship with costs and QALYs, as well as representing a clinical situation where health states change or recurrent events occur over a long period of time. For frail malnourished individuals, there is a high likelihood of health complications which means that the health and cost impact of prolonged periods of time in these adverse health states needs to be captured appropriately. This type of model may be considered more flexible than a patient cohort model, with the individual histories of patients in the model being recorded. The model will incorporate patient heterogeneity, as well as stochastic and parameter uncertainty. Both deterministic and probabilistic sensitivity analyses will be conducted to explore uncertainty in the data used to populate the model, as well as the model structure. The time horizon of the model will be the lifetime of individuals; shorter time horizons will be incorporated if considered meaningful and useful to decision-makers.

Outcomes from the model will also be used to explore future research needs using variants of Value of Information (VoI) analysis including expected value of perfect information and expected value of partial perfect information.[75] These methods will estimate the value of collecting further information to reduce uncertainty around all model parameters and individual, or specific groups of, parameters. VoI methods can be used to estimate the expected gain in net benefit from obtaining additional information for the purpose of decision making. Additionally, it allows for the identification of the specific areas of uncertainty around which further research would be most valuable.

Should the data suggest that there is value in modelling based on both the effectiveness of components (NMA) and meta-regression results from TDF/CFIR domains, and resources allow, the economic model will be adapted and results for both analyses presented and compared.

Phase 3: Collating findings and developing recommendations for research and implications for practice with stakeholders

The purpose of our research is to produce recommendations for future research and implication for practice to prevent and reduce malnutrition risk in frail older people. In order to formulate these implications for future research and practice, we will consider the effectiveness and cost-effectiveness of interventions, and issues related to acceptability and implementation of interventions. To do this we will bring together results from the evidence synthesis (from quantitative and qualitative studies), economic modelling, views of key stakeholders (PPI/E and Review Advisory Group), and finalise the logic model. We will apply cross-study synthesis to bring together results from quantitative and qualitative data.[76] This involves a comparative analysis, which juxtaposes findings from the quantitative and qualitative reviews; the analysis brings together findings to identify appropriate and acceptable interventions which match the needs and views of those targeted by interventions.

Key findings from the study phases will be mapped against the research objectives, including issues of effectiveness, acceptability, settings, adherence, potential adverse effects, cost-effectiveness and value of interventions. We will consider the use of triangulation methods which bring together quantitative and qualitative data.[77] A triangulation protocol offers a helpful aid to identify themes from study findings and identify where there is convergence, agreement or dissonance. We will include a narrative on the concordances and differences between research and stakeholder perspectives.

Our key stakeholders (older people, carers, clinicians, dieticians, charities, policy makers) will be part of this exercise of finalising implications. Recommendations will be developed for design of evidence-based oral nutritional interventions for future research in frail older people; and implications for practice and policy. We will conduct a workshop jointly with our PPI/E Co-applicant from Elders Council to disseminate our findings with stakeholders, and to discuss and agree on implications of our findings. These implications together with the final logic model will be disseminated widely through our network of stakeholders (policy, practice and charities).

6. Dissemination, Outputs and anticipated Impact

Dissemination

Having a range of stakeholders within our team and Advisory Group will enable dissemination and engagement with clinicians, service users and policy makers. We will also hold a workshop in the early phase of the project as a Quarterly Research Meeting of *Fuse, Centre for Translational Research in Public Health*, which is an established network in North-East England of practitioners from NHS, Local Authority, Public Health England and third sector. The PI co-leads the Healthy Ageing programme of Fuse. This early workshop will be used to engage with a wider range of stakeholders with an interest in the health of frail older people. Their views will be used to inform the project (for example, logic model, scope of review) and for early engagement with stakeholders. We will have regular engagement with stakeholders in our Review Advisory Group. These stakeholders include Elders Council Newcastle (Barbara Douglas), Food Nation (charity working to improve nutrition of people at risk of under-nutrition), clinicians leading on frailty and malnutrition (Lesley Bainbridge: Frailty Clinical Network Lead North East & North Cumbria) and secondary care; dieticians (Robyn Collery: NHS Vanguard Programme); and policy makers (Elaine Rashbrook: PHE). Research experts in nutrition and malnutrition will also input into the project (Ashley Adamson, Newcastle; Paul Little, Southampton; Margot Gosney: Reading). This wide network of stakeholders and continuous engagement with them will help with dissemination. We will also conduct a workshop with stakeholders in the final phase of the project to share findings and to collectively formulate recommendations for practice, policy and future research. We will use our stakeholder network to disseminate the final findings widely.

Our team members co-lead (Hanratty) and are co-investigators (Craig) on the NIHR Policy Research Unit (PRU) in Frailty and Older People, and co- investigators (Craig) on PRU in Behavioural Science – these PRUs are well-placed to provide recommendations to the Department of Health & Social Care. The Fuse network is a valuable route for disseminating our research and building wider partnerships with practitioners across health and third sector organisations. Our team (Hanratty, Ramsay, Craig) is also part of the proposed NIHR Applied Research Collaboration in the North East, which has a theme on multi-morbidity and frailty. We will also disseminate our findings through peer-reviewed open access journals and conference presentations.

Outputs and anticipated impact

Key outputs from our research will include evidence that will inform future research and implications for policy and practice. Specific outputs include: a) a logic model that will provide a conceptual framework and underpinning of interventions to reduce malnutrition in frail older people, and where, how and why these interventions work (or not). The logic model will be of value to clinicians, commissioners and policy makers and aid them in decision making around interventions for frail older people. b) Evidence on interventions, including their components, and how, where they are delivered and target populations. c) Evidence on cost-effectiveness of interventions to reduce malnutrition in frail older people; d) Implications for policy and practice for ways to reduce malnutrition risk in frail elderly. These research outputs will be relevant for a range of beneficiaries including researchers developing interventions for frail older people; clinicians in primary and secondary care; older people and carers; charities, and policy makers. Working in partnership with representatives from these groups will enable us to achieve these outputs and impacts. This goal of this project is to inform and develop further interventions that can be evaluated in future research, for example through NIHR Health Technology Assessments or NIHR Health Services & Delivery Research.

Possible barriers for further research and implementation

Possible barriers for further research, development and implementation include issues such as funding for future research or adoption of interventions. Concrete steps will need to be taken to ensure that implementation and adoption is embedded into further research and development of implementation. Evidence from this proposed project will shed light on these critical issues related to implementation, delivery and sustainability of interventions and views of stakeholders – an in-depth understanding of these issues will help strengthening the potential for implementation of future research.

7. Project / research timetable

The project will be conducted over 18 months as follows (project outline in Figure 3 and Gantt chart in Figure 4 below):

Months 1-4: Stakeholder and PPI/E engagement, protocol development, search strategy developed and piloted, protocol submitted to PROSPERO.
Milestones (MS1 in Gantt chart uploaded): protocol submitted to PROSPERO, stakeholder engagement meeting.

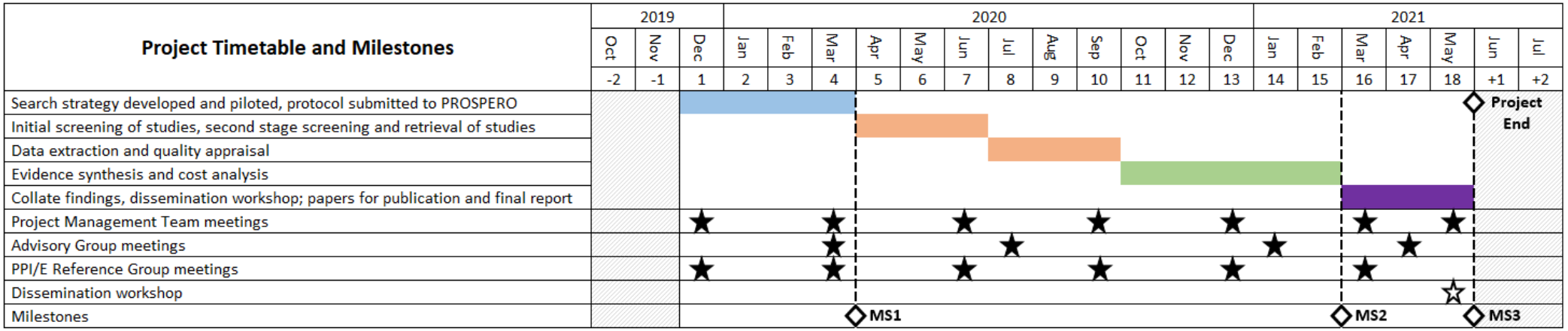
Months 5-7: initial screening of studies, second stage screening, retrieval of studies, first draft of economic model structure and analysis plan.

Months 8-10: data extraction, data coding using TDF and CFIR taxonomy, quality appraisal, refinement of economic model and analysis plan.

Months 11-15: meta-regression analysis, evidence synthesis and economic analysis.
Milestones (MS2): Completion of evidence synthesis of and economic analysis; draft paper for publication.

Months 16-18: collate findings, dissemination and stakeholder workshop; papers for publication and final report. Logic model will be refined and developed at all stages of the project.
Milestones (MS3): Final logic model; recommendations; workshop for dissemination; papers; conference presentations.

Figure 4: Project Gantt chart



8. Project management

The sponsor of our research will be Newcastle University. A project management team will meet regularly (every 3 months) including the Principal Investigator (PI, Ramsay), PPI/E co-applicant (Raffle) and the other co-applicants. The PI will lead the project and will be responsible for the overall management of the project, ensuring that it runs to time and as planned. Craig will oversee the methodological aspects of the evidence synthesis and economic analysis. Raffle will lead the PPI/E input. McEvoy and Hanratty will offer particular input and expertise in nutritional interventions and frailty into the systematic review element of the project.

The regular project meetings will be used to monitor the progress of the project and to ensure continuous input from PPI/E group through our Co-applicant (Raffle). The PPI/E Reference Group (chaired by Raffle) and Review Advisory Group (chaired by Ramsay) will meet at all stages of the project. The milestones in our project timetable will be used to plan and assess the progress of the project delivery.

9. Ethics

Ethical approval will not be required since this project does not involve any primary research.

10. Patient and Public Involvement and engagement (PPI/E)

Our project reflects engagement with older people and carers both in the development of this proposal and in the project plans. Our preparatory PPI/E consultations conducted with older people and carers and our co-applicant (Raffle, Elders Council) have provided direct inputs into the project – for example, they highlighted that compliance, social support, access to resources, socioeconomic factors, acceptability, and affordability are important issues that need to be considered for reducing malnutrition; we have included these factors in our initial logic model. We have also included these issues as key factors that will be investigated in the systematic review of qualitative and mixed-methods studies. The PPI/E consultation also pointed out the need for feeding back older people's views into research findings and for engaging with policy and practice. We have included plans for this through our PPI/E Reference Group. We also developed our lay summary with comments from 11 members (older people) from Voice, a national organisation that presents public/ patient views and opinions.

We have plans for engaging with older people at all stages of the project through our PPI/E Reference Group, which will be led by our PPI/E Co-applicant (Raffle). This group of five older people will meet periodically during the project and contribute to all project phases, including the scope of the review, emerging findings, interpretation of results, refining the logic model and dissemination. We have included costs for the regular PPI/E group meetings towards their time and travel. Bespoke training for PPI/E members will be provided at Newcastle University. Raffle and the PPI/E group will also help in the planning and delivery of the dissemination workshop with wider network of stakeholders.

We will engage with other stakeholders, including clinicians in primary and secondary care with an interest in frailty through our links with the Academic Health Sciences Network through Lesley Bainbridge who leads the Frailty Clinical Network in North East & North Cumbria. We will also consult with dieticians (Robyn Collery: dietician NHS Vanguard Programme) and policy makers in PHE (Elaine Rashbrook) who are part of our Review Advisory Group.

11. Project / research expertise

Our team is inter-disciplinary with expertise from public health, clinicians, frailty, nutrition, evidence synthesis, and health economics. Ramsay (Principal Investigator) is a public health specialist with expertise in frailty, health inequalities, epidemiology and ageing research. She co-leads the Healthy Ageing theme of Fuse, Centre for Translational Public Health Research, North-East England. Raffle (PPI/E co-applicant) has valuable expertise as an older person/ service user. Craig has extensive experience in evidence synthesis and health economics; she leads the Evidence Synthesis Group,

co-leads the Health Economics & Evidence Synthesis Theme at Newcastle University and is Co-Director of the NIHR Innovation Observatory. McEvoy is a dietician with expertise in epidemiology and nutritional interventions in older people. Hanratty is a General Practitioner and public health specialist with expertise in frailty and Co-Director of the Policy Research Unit in Older People & Frailty. Tanner has expertise in evidence synthesis. Moloney has expertise in health economics. Gosney (collaborator) has expertise as a clinician in elderly medicine and research expertise in malnutrition in older people. Adamson (collaborator) has expertise in dietetics, public health nutrition and developing nutritional interventions. Little (collaborator) will provide specific expertise interventions for malnutrition.

12. Success criteria and barriers to proposed work

The project aims to generate evidence that will inform future research, and implications for practice and policy to reduce malnutrition in frail older people. It will provide insights into evidence on effective and cost-effective oral nutritional interventions as well their components and factors affecting acceptability and adherence. Success criteria will include achieving milestones as set out in our project plan, such as submission of review protocols, completion of evidence synthesis and economic analysis. Regular input from and engagement with stakeholders (older people, carers, clinicians, dieticians, policy makers) will be another important marker of success. A logic model based on the evidence synthesis and input from stakeholders will be an important output to guide further research and practice, and will be another success criteria. The research team is collectively well-placed to meet these milestones with experience of undertaking complex public health research and evidence synthesis including HTA projects.

A potential barrier in systematic reviews is the lack of sufficient evidence to review. However, our scoping search demonstrates a sizeable evidence base that lends itself to a systematic review and evidence synthesis. It is also possible that the evidence base is larger than anticipated. However, our scoping search has helped us plan our project according to the likely size of the evidence base. If we find a larger than anticipated evidence base, we will consider amending our inclusion criteria, for example to restrict to certain types of RCTs. We will also consider principles that will guide these choices which will be set out in the protocol developed in the initial phase of the project.

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